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ORIGINAL INVESTIGATIONS

Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort

A Long-Term Follow-Up Study (LEGACY)

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ABSTRACT

BACKGROUND Obesity and atrial fibrillation (AF) frequently coexist. Weight loss reduces the burden of AF, but whether this is sustained, has a dose effect, or is influenced by weight fluctuation is unknown.

OBJECTIVES This study sought to evaluate the long-term impact of weight loss and weight fluctuation on rhythm control in obese individuals with AF.

METHODS Of 1,415 consecutive patients with AF, 825 had a body mass index ≥27 kg/m^2 and were offered weight management. After screening for exclusion criteria, 355 were included in this analysis. Weight loss was categorized as group 1 (≥10%), group 2 (3% to 9%), and group 3 (<3%). Weight trend and/or fluctuation was determined by yearly follow-up. We determined the impact on the AF severity scale and 7-day ambulatory monitoring.

RESULTS There were no differences in baseline characteristics or follow-up among the groups. AF burden and symptom severity decreased more in group 1 compared with groups 2 and 3 ($p < 0.001$ for all). Arrhythmia-free survival with and without rhythm control strategies was greatest in group 1 compared with groups 2 and 3 ($p < 0.001$ for both). In multivariate analyses, weight loss and weight fluctuation were independent predictors of outcomes ($p < 0.001$ for both). Weight loss ≥10% resulted in a 6-fold (95% confidence interval: 3.4 to 10.3; $p < 0.001$) greater probability of arrhythmia-free survival compared with the other 2 groups. Weight fluctuation >5% partially offset this benefit, with a 2-fold (95% confidence interval: 1.0 to 4.3; $p = 0.02$) increased risk of arrhythmia recurrence.

CONCLUSIONS Long-term sustained weight loss is associated with significant reduction of AF burden and maintenance of sinus rhythm. (Long-Term Effect of Goal directed weight management on Atrial Fibrillation Cohort: A 5 Year follow-up study [LEGACY Study]; ACTRN12614001123639) (J Am Coll Cardiol 2015;65:2159–69) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AFSS = Atrial Fibrillation Severity Scale

AHI = apnea-hypopnea index

BMI = body mass index

BP = blood pressure

hsCRP = high-sensitivity C-reactive protein

IVS = interventricular septum

LA = left atrium

Recent epidemiological data confirmed the emergence of obesity and atrial fibrillation (AF) as global epidemics (1,2). In the United States, the prevalence of obese individuals has risen 3-fold since 1960, with 1 in every 3 persons being obese (3). If such trends continue unabated, it is estimated that 164 million Americans will be obese by 2030, with an additional health care cost of $66 billion annually (4,5). The prevalence of AF is projected to reach 15.9 million in the United States by 2050 (2,6,7). Because obesity is independently associated with AF, these dual epidemics confer an enormous management and economic burden (8–11).

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Obesity and its associated cardiometabolic comorbidities, such as hypertension, diabetes mellitus, and sleep apnea have been proposed as contributors to the expanding epidemic of AF (8,12,13), and are thus potential targets for intervention to stem the expanding AF epidemic. Weight loss in the short term results in a reduction in the symptomatic AF burden (14). Recent data demonstrated that aggressive weight and risk factor management improves maintenance of sinus rhythm after AF ablation (15).

Whether a critical weight loss threshold is required, or if benefits conferred by the initial weight loss are sustained in the long term is unknown. Furthermore, obese individuals frequently oscillate in weight over time, and the impact of such weight fluctuation on the arrhythmia burden is not known. We hypothesized that weight loss, if sustained, will be of incremental benefit in rhythm control. In this study, we assess the long-term impact of weight loss and weight fluctuation on rhythm control in obese individuals with AF.

METHODS

STUDY POPULATION. The study included consecutive patients who were referred for management of symptomatic paroxysmal or persistent AF to the Centre for Heart Rhythm Disorders at the University of Adelaide, Adelaide, Australia. All patients with a body mass index (BMI) ≥27 kg/m^2 were included in this analysis. Exclusion criteria were permanent AF, history of myocardial infarction or cardiac surgery in the previous 12 months, significant cardiac valvulopathy or ventricular dysfunction, active malignancy, autoimmune or systemic inflammatory diseases, severe renal or hepatic failure, and <24 months of follow-up.

The study protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and University of Adelaide, Adelaide, Australia.

STUDY PROTOCOL AND DESIGN. All patients were counseled on the importance of weight and risk factor management, with optional participation in a dedicated physician-led weight management clinic or self-managed weight loss program.

Weight management. The weight and other risk factor management protocols have been presented previously and are outlined in the Online Appendix (15). In brief, a structured motivational and goal-directed program using face-to-face counseling was used for weight reduction. Patients were reviewed regularly (every 3 months in the initial phase), and encouraged to use support counseling and schedule more frequent reviews as required. Initial weight reduction was attempted by a meal plan and behavior modification. Participants were required to maintain a diet and physical activity diary. Meals consisted of high protein and low glycemic index, calorie-controlled foods. If patients lost <3% of weight after 3 months, they were then prescribed very-low-calorie meal replacement sachets (Prima Health Solutions,

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New South Wales, Australia, or Nestle Health Science, Vevey, Switzerland) for 1 to 2 meals/day. The initial goal was to reduce body weight by 10%. After patients achieved the initial goal, meal replacement was substituted to high protein and low glycemic index, calorie-controlled foods to achieve a target BMI of ≤25 kg/m^2. Low-intensity exercise was prescribed initially for 20 min thrice weekly and increasing to at least 200 min of moderate-intensity activity per week. Hypertension, glucose intolerance, sleep apnea, alcohol, and tobacco use were screened for and managed individually according to American Heart Association/American College of Cardiology guidelines. Changes in metabolic (lipid profile and fasting insulin) and inflammatory state (high-sensitivity C-reactive protein hsCRP) levels were monitored.

Weight loss definition. A stadiometer and digital weighing machine were used to record height and weight in light clothing without shoes, and BMI was calculated. Anthropometric values measured at annual follow-up were utilized for weight loss and weight fluctuation assessment. The American Heart Association/American College of Cardiology guidelines recognize that any weight loss ≥3% is considered a meaningful reduction (16). To determine the dose-response effect of weight loss on AF burden, groups were divided as follows: ≥10% weight loss (group 1), 3% to 9% weight loss (group 2), and <3% weight loss or weight gain (group 3).

Weight trend definition. Weight trend was determined by percentage change in annual weight over the course of the study. Linear weight loss was defined by continuous weight loss at each annual follow-up with no interim weight gain of ≥1%. Linear weight gain was defined by continuous weight gain at each annual follow-up with no interim weight loss of ≥1%. Weight fluctuation was defined by ≥1% weight cycle ("gain-loss" or "loss-gain") between 2 consecutive annual follow-ups.

Quantification of weight fluctuation. To assess the effect of the magnitude of weight fluctuation, patients were divided on the basis of yearly follow-ups: >5% weight fluctuation (wide), 2% to 5% weight fluctuation (average), and <2% weight fluctuation (stable).

Arrhythmia management. Management of AF was undertaken in a dedicated AF clinic independent of the weight management clinic. Usage of rate and rhythm control strategies was at the treating physician's discretion. The drugs used for rhythm control included sotalol or flecainide. Amiodarone was not usually used. Ablation was advocated in patients who remained symptomatic despite use of antiarrhythmic drugs. The ablation technique used at our institution was previously described and is outlined in the Online Appendix (17). AF was determined at least annually by clinical review, 12-lead electrocardiogram, and 7-day Holter monitoring. In patients who underwent ablation, procedural success was determined after a 3-month blanking period. AF was considered any atrial arrhythmia ≥30 s. The earliest date with documented AF was set as the date of arrhythmia recurrence.

Cardiac structural parameters were monitored by serial echocardiographic examinations. All echocardiographic and rhythm evaluations are detailed in the Online Appendix and performed by operators blinded to the patient's weight management regimen.

OUTCOMES. The primary outcome was AF burden as determined by symptom burden and AF freedom. AF symptom burden was determined by the AF Severity Scale (AFSS) (University of Toronto, Toronto, Ontario, Canada), which quantitates 3 domains of AF-related symptoms: frequency, duration, and severity (18). The AFSS has been clinically validated and used for assessment of AF burden (14,15). In addition, it provides a symptom subscale and global well-being score. The AFSS questionnaire was administered at baseline and final follow-up. AF freedom was determined with 7-day Holter monitoring. Secondary outcomes included structural parameters of left atrial volume and left ventricular wall thickness from echocardiographic studies.

Statistical analysis. Categorical variables are represented by frequencies and percentages. Continuous variables are summarized by mean ± SD. Differences between the weight loss groups were assessed using analysis of variance procedures for baseline characteristics. A repeated measure analysis of variance was used to assess change over time. For categorical variables, change in status at follow-up was compared between groups using a chi-square test. Time-to-recurrence and event-free survival curves following the last ablation procedure were estimated by the Kaplan-Meier product-limit method. Differences between curves were tested with the log-rank test. Predictors of recurrent AF were assessed using proportional hazards Cox regression models. Candidate variables with $p < 0.1$ in univariate analyses were considered in multivariate regression models. Two-tailed $p < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS version 21.0 (SPSS, Inc., Chicago, Illinois).

RESULTS

BASELINE CHARACTERISTICS. Of 1,415 consecutive patients with symptomatic AF, 825 patients had a BMI

of ≥27 kg/m². After screening for exclusion criteria, the final cohort consisted of 355 patients (Figure 1): 135 in group 1 (≥10% weight loss), 103 in group 2 (3% to 9% weight loss), and 117 in group 3 (<3% weight-loss). Baseline characteristics and follow-up duration (48.4 ± 18.2, 46.0 ± 16.7, and 48.3 ± 18.4 months, respectively; p = 0.3) were similar for all groups (Table 1).

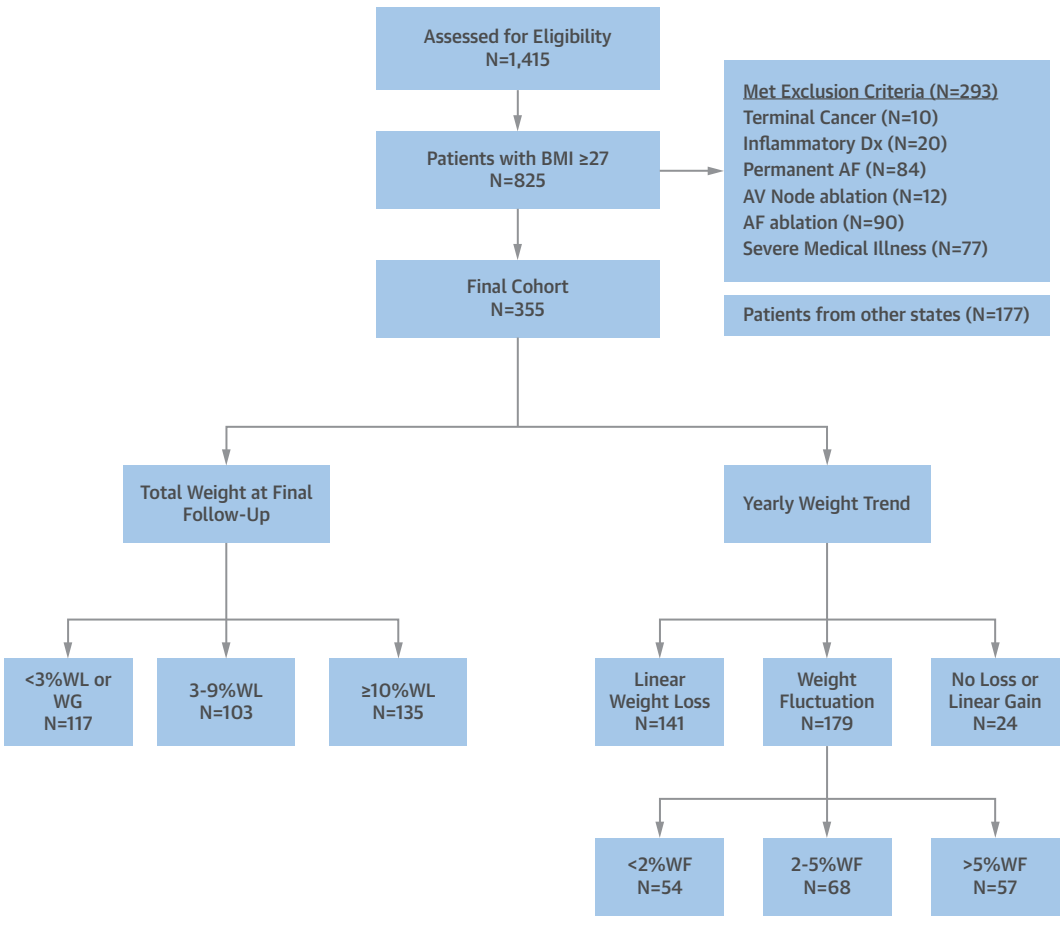
WEIGHT LOSS AND MAINTENANCE. Weight change was greater in group 1 than in groups 2 and 3 (-16.0 ± 3.0 kg vs. -6.0 ± 0.4 kg vs. +2.0 ± 1.0 kg, respectively; p < 0.001). This corresponded with higher participation in the dedicated weight management clinic (84% in group 1 vs. 57% in group 2 vs. 30% in group 3; p < 0.001). The weight loss was largely durable over time with 66% (34 of 52 patients) who lost ≥10% body weight in the first year maintaining their weight loss at 34.5 ± 15.5 months. Importantly, 85% of these patients attended the weight management clinic (p < 0.001). In contrast, only 2 of the 18 patients who had regained weight after initial weight loss of ≥10% in the first year attended the weight management clinic.

EFFECT OF WEIGHT LOSS ON RISK FACTOR PROFILE. Table 2 shows the impact of weight management on various cardiac risk factors.

Blood pressure control. There was a stepwise improvement in mean systolic blood pressure (BP) with weight loss (−18.0 ± 5.0 mm Hg vs. −10.0 ± 3.0 mm Hg vs. −7.0 ± 2.0 mm Hg for groups 1, 2, and 3 respectively; p < 0.001). This was despite reduced, unchanged, and increased antihypertensive agent use in groups 1, 2, and 3, respectively (p = 0.037).

Lipid management. A greater reduction in low-density cholesterol, triglycerides, and total cholesterol levels was seen in group 1 compared with groups

FIGURE 1 Patient Selection



Flow diagram demonstrating patient recruitment and attrition. AF = atrial fibrillation; AV = aortic valve; BMI = body mass index; Dx = diagnosis; WF = weight fluctuation; WG = weight gain; WL = weight loss.

2 and 3 ($p < 0.001$) in conjunction with reduced use of lipid-lowering therapy ($p = 0.04$).

Glycemic control. Diabetic patients demonstrated improved glycemic control (glycosylated hemoglobin <7%) from group 3 to group 2 to group 1 ($p < 0.001$). This was in conjunction with a decrease in fasting insulin in group 1 ($p < 0.001$) and group 2 ($p = 0.06$) as opposed to an increased insulin level in group 3 ($p = 0.03$).

Inflammation. Patients in groups 1 and 2 demonstrated a decrease in mean hsCRP ($p < 0.001$ and $p = 0.004$, respectively) as opposed to increased hsCRP levels in group 3 ($p = 0.001$).

EFFECT OF WEIGHT LOSS ON CARDIAC STRUCTURE. Table 2 shows the effect of weight loss on cardiac structure. Left atrial volume indexed for body surface area decreased significantly with weight loss in group 1 ($p < 0.001$) and group 2 ($p < 0.001$), yet increased in group 3 ($p = 0.02$). Likewise, interventricular septal (IVS) thickness decreased significantly with weight loss in both group 1 ($p = 0.001$) and group 2 ($p = 0.03$), but remained unchanged in group 3 ($p = 0.33$). A similar trend was seen in left ventricular end-diastolic diameter and E/E′ for group 1 and group 2, with subjects in group 3 showing an increasing E/E′ ($p = 0.001$).

EFFECT OF WEIGHT LOSS ON ATRIAL FIBRILLATION SYMPTOM BURDEN. AF frequency, duration, symptoms, and symptom severity were improved in groups 1 and 2 compared with group 3 ($p < 0.001$) (Table 2). The global well-being score improved by 5.9 ± 0.9 in group 1 and was higher than in groups 2 and 3 ($p < 0.001$).

Freedom from AF without the use of rhythm control strategies. Figure 2A demonstrates the "ablation and drug free" AF freedom. At final follow-up, 45.5% of group 1, 22.2% of group 2, and 13.4% of group 3 ($p < 0.001$) remained free from arrhythmia without antiarrhythmic drugs or ablation. Univariate predictors of AF recurrence were the following: group 2 ([compared to group 1]: hazard ratio [HR]: 1.8; 95% confidence interval [CI]: 1.3 to 2.5); group 3 ([compared to group 1]: HR: 2.1; 95% CI: 1.6 to 3.0; $p < 0.001$); interventricular septal thickness (HR: 0.44; 95% CI: 0.23 to 0.86; $p = 0.01$); and E/E′ ratio (HR: 1.4; 95% CI: 1.2 to 1.7; $p < 0.001$). On multivariate analysis, group 2 (compared to group 1): HR: 2.0; 95% CI: 1.4 to 2.9, and group 3 (compared to group 1): HR: 3.0; 95% CI: 2.0 to 4.3; $p < 0.001$), IVS (HR: 0.2; 95% CI: 1.1 to 2.1; $p < 0.001$), and E/E′ ratio (HR: 1.5; 95% CI: 1.2 to 1.9; $p < 0.001$) remained independent predictors of AF recurrence.

Total arrhythmia-free survival. Figure 2B demonstrates the total arrhythmia-free survival with significant attrition in group 3 compared with groups 1 and 2. At final follow-up, total arrhythmia-free survival rates were 86.2% in group 1 compared with 65.5% in group 2 and 39.6% in group 3 ($p < 0.001$). There were no differences in the mean number of ablation procedures among the 3 groups ($p = 0.8$). At final follow-up, the mean number of antiarrhythmic

TABLE 1 Baseline Characteristics

	≥10% WL Group 1 (N = 135)	3%–9% WL Group 2 (N = 103)	<3% WL Group 3 (N = 117)	p Value
Age, yrs	65 ± 11	63 ± 11	61 ± 11	0.06
Male	86 (64)	65 (63)	83 (71)	0.37
WL clinic attendance	114 (84)	59 (57)	35 (30)	<0.001
Anthropometric measures and blood pressure				
Weight, kg	101.3 ± 17.0	98.7 ± 16.4	100.2 ± 16.8	0.52
BMI, kg/m^2	33.6 ± 4.7	32.7 ± 4.4	32.9 ± 4.8	0.24
SBP, mm Hg	147 ± 17	144 ± 17	146 ± 17	0.33
Atrial fibrillation				
Paroxysmal	71 (53)	57 (55)	60 (52)	0.86
Nonparoxysmal	64 (47)	46 (45)	45 (56)	
Metabolic risk factors				
Hypertension	109 (81)	75 (73)	90 (78)	0.30
DM	41 (30)	28 (27)	34 (29)	0.35
IGT	18 (13)	8 (8)	8 (7)	
Hyperlipidemia	66 (49)	45 (44)	56 (48)	0.70
Coronary artery disease	21 (16)	12 (12)	11 (9)	0.31
Valvulopathy	8 (6)	3 (3)	8 (7)	0.41
AHI >30	69 (51)	52 (50)	61 (52)	0.97
Alcohol excess (>30 g/week)	42 (31)	35 (34)	34 (29)	0.73
Smoker	50 (37)	41 (40)	47 (40)	0.86
Medication use				
Antiarrhythmic	1.1 ± 0.7	1.0 ± 0.7	0.9 ± 0.8	0.10
Antihypertensive	1.0 ± 0.9	1.0 ± 0.8	1.1 ± 1.0	0.08
Serology and lipid profile				
hsCRP, mg/l	5.1 ± 9.2	4.4 ± 5.8	4.1 ± 2.9	0.70
Fasting insulin level, mU/l	18.1 ± 6.7	16.6 ± 6.3	18.1 ± 7.0	0.10
LDL level, mg/l	112 ± 38	116 ± 35	104 ± 35	0.20
HDL level, mg/l	46 ± 15	46 ± 15	42 ± 12	0.11
TG level, mg/l	141 ± 62	141 ± 53	141 ± 62	0.78
Total cholesterol, mg/l	189 ± 37	185 ± 42	181 ± 42	0.50
Echocardiographic measures				
LA volume indexed, mls/m^2	37.6 ± 5.4	38.5 ± 6.2	39.0 ± 3.8	0.20
LV IVS, mm	11.7 ± 2.0	11.5 ± 2.0	11.5 ± 2.0	0.24
LVEDD, cm	5.0 ± 0.6	5.0 ± 0.6	5.0 ± 0.6	0.92
E/E′ ratio	12.7 ± 4.2	12.0 ± 4.6	11.3 ± 3.7	0.06
Atrial Fibrillation Severity Scale				
Frequency (1-10)	7.0 ± 1.6	7.0 ± 1.3	7.0 ± 1.7	0.97
Duration (1-10)	7.1 ± 1.8	6.7 ± 1.8	6.9 ± 1.7	0.21
Severity (1-10)	7.0 ± 1.9	7.1 ± 1.5	6.8 ± 1.5	0.50
Symptom (0-35)	19.0 ± 5.9	18.1 ± 4.9	17.7 ± 5.6	0.19
Global well-being (1-10)	2.7 ± 0.8	2.4 ± 0.9	2.5 ± 0.9	0.4

Values are mean ± SD or n (%).

AHI = apnea-hypopnea index; BMI = body mass index; DM = diabetes mellitus; HDL = high-density lipoprotein; hsCRP = high-sensitive C-reactive protein; IGT = impaired glucose tolerance; LA = left atrium; LDL = low-density lipoprotein; LVEDD = left ventricular end-diastolic diameter; LV IVS = left ventricular interventricular septum; SBP = systolic blood pressure; TG = triglyceride; WL= weight loss.

TABLE 2 Weight Loss

	≥10% WL Group (N = 135)			3%-9% WL Group (N = 103)			< 3% WL Group (N = 117)			
	Baseline	Follow-Up‡	p Value*	Baseline	Follow-Up‡	p Value*	Baseline	Follow-Up‡	p Value*	p Value†
Weight, kg	101 ± 17	85 ± 14	<0.001	99 ± 16	93 ± 16	<0.001	100 ± 17	102 ± 18	<0.001	<0.001
BMI, kg/m^2	33.7 ± 4.7	28.4 ± 4.0	<0.001	32.7 ± 4.4	30.8 ± 4.2	<0.001	33.0 ± 4.9	33.5 ± 5.3	<0.001	<0.001
Mean SBP, mm Hg	147 ± 17	129 ± 12	<0.001	144 ± 17	134 ± 14	<0.001	146 ±17	139 ± 15	<0.001	<0.001
DM with HbA$_{1c}$ ≥7	40 (30)	5 (4)	–	28 (27)	15 (15)	–	34 (29)	23 (20)	–	<0.001
Medication use										
Anti-HTN	1.0 ± 0.9	0.5 ± 0.6	<0.001	0.7 ± 0.8	0.7 ± 0.6	0.74	0.8 ± 1.0	1.0 ± 0.7	0.01	<0.001
On lipid Rx	66 (49)	37 (27)	–	45 (44)	38 (37)	–	56 (48)	54 (46)	–	<0.001
AAD	1.1 ± 0.7	0.1 ± 0.4	<0.001	1.0 ± 0.7	0.5 ± 0.6	<0.001	0.8 ± 0.8	0.4 ± 0.6	<0.001	<0.001
Serology and lipid profile										
hsCRP, mg/l	5.1 ± 9.2	1.2 ± 2.4	<0.001	4.4 ± 5.8	2.7 ± 3.2	0.004	4.1 ± 2.9	4.9 ± 5.0	0.001	<0.001
Fasting insulin, mU/l	18.3 ± 6.6	8.4 ± 3.9	<0.001	16.9 ± 6.1	14.8 ± 9.4	0.06	14.5 ± 6.9	17.3 ± 9.6	0.03	<0.001
LDL level, mg/dl	116 ± 37	89 ± 31	<0.001	116 ± 35	93 ± 23	<0.001	104 ± 35	108 ± 31	0.05	<0.001
HDL level, mg/dl	50 ± 15	58 ± 15	<0.001	46 ± 11	50 ± 11	0.01	42 ± 11	46 ± 11	0.79	<0.001
TG level, mg/dl	141 ± 62	97 ± 35	<0.001	141 ± 53	115 ± 53	<0.001	141 ± 62	159 ± 62	0.03	<0.001
Total cholesterol, mg/dl	189 ± 38	158 ± 35	<0.001	185 ± 42	162 ± 27	<0.001	178 ± 42	178 ± 35	0.51	<0.001
Echocardiogram										
Indexed LA volume, ml/m^2	37.6 ± 5.4	30.9 ± 6.4	<0.001	39.5 ± 6.2	34.7 ± 10.0	<0.001	39.0 ± 3.8	40.4 ± 5.9	0.02	<0.001
IV septum, mm	11.7 ± 2.0	10.1 ± 0.7	0.001	11.5 ± 2.0	10.9 ± 2.0	0.03	11.5 ± 2.0	11.4 ± 2.0	0.33	<0.001
LVEDD, cm	5.0 ± 0.6	4.6 ± 0.9	<0.001	5.0 ± 0.6	4.9 ± 0.7	0.01	5.0 ± 0.6	5.0 ± 0.6	0.82	<0.001
E/E' ratio	12.8 ± 4.2	8.5 ± 3.3	<0.001	11.9 ± 4.6	9.1 ± 3.2	<0.001	11.6 ± 3.5	13.7 ± 5.4	0.001	<0.001
AF symptom score										
AF frequency (1-10)	7.0 ± 1.5	3.0 ± 1.9	<0.001	7.0 ± 1.3	3.7 ± 1.7	<0.001	7.1 ± 1.5	4.6 ± 1.6	<0.001	<0.001
AF duration (1.25-10)	7.1 ± 1.8	4.2 ± 2.5	<0.001	6.7 ± 1.8	4.9 ± 2.4	<0.001	6.8 ± 1.7	5.4 ± 2.1	<0.001	<0.001
AF episode severity (1-10)	7.0 ± 1.9	3.3 ± 1.8	<0.001	7.1 ± 1.4	4.3 ± 2.0	<0.001	6.8 ± 1.5	5.4 ± 2.1	<0.001	<0.001
AF symptom subscale (0-35)	19.1 ± 5.9	9.2 ± 5.0	<0.001	18.1 ± 4.9	11.1 ± 4.9	<0.001	18.2 ± 5.1	13.6 ± 4.4	<0.001	<0.001
Global well-being (1-10)	2.7 ± 0.8	8.1 ± 1.2	<0.001	2.4 ± 0.9	6.1 ± 0.9	<0.001	2.5 ± 0.9	5.7 ± 2.0	0.001	<0.001

Values are mean ± SD or n (%). Impact of weight loss on cardiac risk factors, cardiac structure, and atrial fibrillation (AF) severity from baseline to follow-up. *p Value refers to within group difference (baseline to follow-up). †p Value refers to between group differences over time (group-time interaction). ‡Median follow-up: 48.4 ± 18.2 months for group 1, 46.0 ± 16.7 months for group 2, and 48.3 ± 18.4 months for group 3.

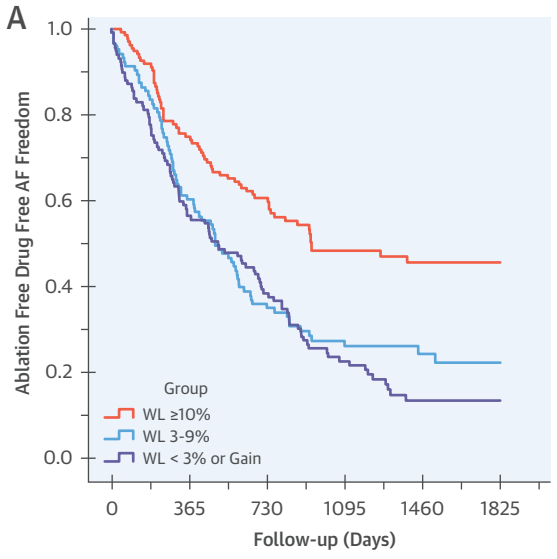
AAD = antiarrhythmic drug; HbA$_{1c}$ = glycosylated hemoglobin; HTN = hypertension; Rx = prescription; other abbreviations as in Table 1.

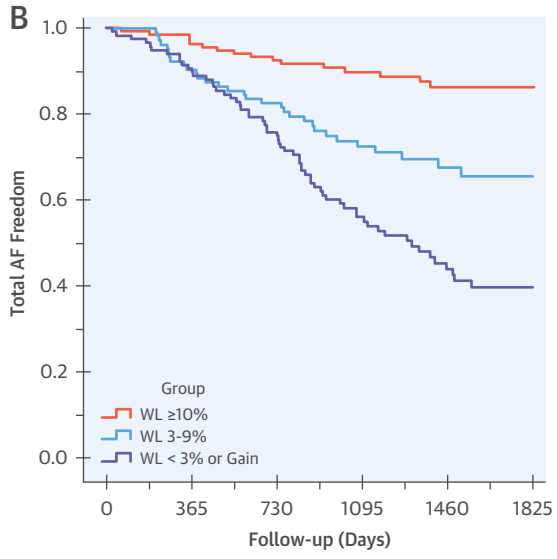
drug use was significantly lower in group 1 compared with groups 2 and 3 ($p < 0.001$). Univariate predictors of AF recurrence were the following: group 2 ([compared to group 1]: HR: 2.8; 95% CI: 1.5 to 5.2); group 3 ([compared to group 1]: HR: 5.5; 95% CI: 3.1 to 9.6; $p < 0.001$); diabetes (HR: 1.6; 95% CI: 1.1 to 2.3; $p = 0.013$); and current smoking status (HR: 1.4; 95% CI: 1.0 to 2.1; $p = 0.048$). On multivariate analysis, group 2 ([compared to group 1]: HR: 3.1; 95% CI: 1.7 to 5.6; $p < 0.001$); group 3 ([compared to group 1]: HR: 5.9; 95% CI: 3.4 to 10.3; $p < 0.001$) and history of diabetes (HR: 1.8; 95% CI: 1.2 to 2.7; $p = 0.002$) remained independent predictors of AF recurrence.

Effect of weight loss trend. Of 355 patients, 141 had linear weight loss, 24 had linear weight gain, and 179 had weight fluctuation. Eleven patients were excluded from analysis, due to missing yearly weight data. Figure 3 demonstrates total arrhythmia-free survival on the basis of weight change trends. At final follow-up, 76% of patients with linear weight loss remained free of arrhythmia ($p < 0.001$). Weight fluctuation offset some of the benefit conferred by weight loss, with 59% patients remaining free from AF. However, this remained higher than the no weight loss or weight gain group, where only 38% remained free of AF ($p < 0.001$).

Effect of weight fluctuation. Of 179 patients with weight fluctuation during the annual follow-ups, 54 had ≤2%, 68 had 2% to 5%, and 57 had >5% weight fluctuation. Patients attending the dedicated weight management clinic had smaller weight fluctuation: 69% of the <2% group, 55% of the 2% to 5% group, and 30% of the >5% weight fluctuation group ($p < 0.001$). Table 3 shows the impact of weight fluctuation on various cardiometabolic risk factors. More than 5% weight fluctuation was associated with significantly increased requirement of antihypertensive medication ($p = 0.04$). Significantly lower systolic BP was seen in patients with <2% weight fluctuation

FIGURE 2 Atrial Fibrillation Freedom Outcome According to Group





Time (Days)	0	365	730	1095	1460	1825
≥10 WL	135	101	72	42	31	18
3-9% WL	103	62	36	22	13	7
<3% WL or gain	117	66	44	22	11	9

0	365	730	1095	1460	1825
135	130	114	86	67	36
103	93	83	57	35	22
117	105	85	53	32	22

(A) Kaplan-Meier curve for AF-free survival without the use of rhythm control strategies. **(B)** Kaplan-Meier curve for AF-free survival for total AF-free survival (multiple ablation procedures with and without drugs). Abbreviations as in Figure 1.

compared with 2% to 5% weight fluctuation and >5% weight fluctuation groups. Mean fasting insulin ($p = 0.01$), hsCRP level ($p = 0.05$), and serum low-density lipoprotein cholesterol ($p < 0.001$) levels were significantly higher in patients with >5% weight fluctuation. Similarly, >5% weight fluctuation was associated with an adverse impact on cardiac structural remodeling, with left atrial volume indexed for body surface area, IVS, and left ventricular end-diastolic diameter remaining largely unchanged compared with patients with <5% weight fluctuation.

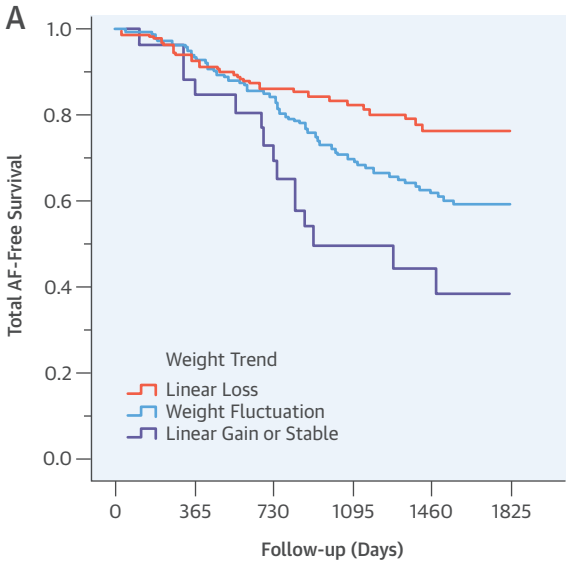
Figure 3 shows total arrhythmia-free survival on the basis of degree of weight fluctuation, with significant attrition seen with >5% compared with ≤5% weight fluctuation. At final follow-up, 85.2% of patients with <2% weight fluctuation, 59% with 2% to 5% weight fluctuation, and 44% with >5% ($p < 0.001$) remained arrhythmia free. After adjustment for baseline BMI, the effect of weight fluctuation remained statistically significant for total AF recurrence ($p = 0.03$). On multivariate analysis, >5% weight fluctuation was associated with an increased risk of AF recurrence compared with <2% weight fluctuation (HR: 2.06, 95% CI: 1.0 to 4.3; $p = 0.02$).

DISCUSSION

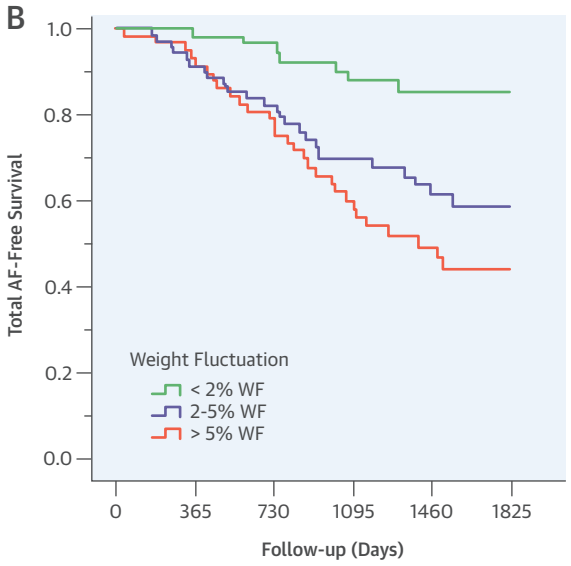
This study demonstrates that in overweight and obese individuals with symptomatic AF, progressive weight loss has a dose-dependent effect on long-term freedom from AF (Central Illustration). Long-term weight loss maintenance is achievable in these patients and is associated with a 6-fold greater freedom from AF. Notably, weight fluctuation of >5% had an adverse effect on overall freedom from AF, with a 2-fold greater likelihood of recurrent arrhythmia. Weight loss was also associated with beneficial structural remodeling, including significant reductions in left atrial volumes and left ventricular hypertrophy. Importantly, achieving and maintaining weight loss was facilitated by a dedicated physician-led clinic that was focused on the management of weight and risk factors. These findings underscore the importance of treating underlying causative conditions when attempting to maintain sinus rhythm in obese AF patients.

Epidemiological data have shown an incremental risk of AF with a progressive increase in BMI (8).

FIGURE 3 Outcomes of Atrial Fibrillation Freedom According to Weight Trend and Weight Fluctuation



Time (Days)	0	365	730	1095	1460	1825
Linear Loss	141	130	122	80	52	29
Fluctuation	179	165	140	99	71	44
Linear Gain	24	20	18	12	8	5



Time (Days)	0	365	730	1095	1460	1825
< 2% WF	54	52	49	39	33	19
2-5% WF	68	62	54	39	27	15
> 5% WF	57	53	45	31	19	14

(A) Kaplan-Meier curve for total AF-free survival (multiple ablation procedures with and without drugs) according to weight trend. **(B)** Kaplan-Meier curve for total AF-free survival (multiple ablation procedures with and without drugs) according to weight fluctuation. Abbreviations as in Figure 1.

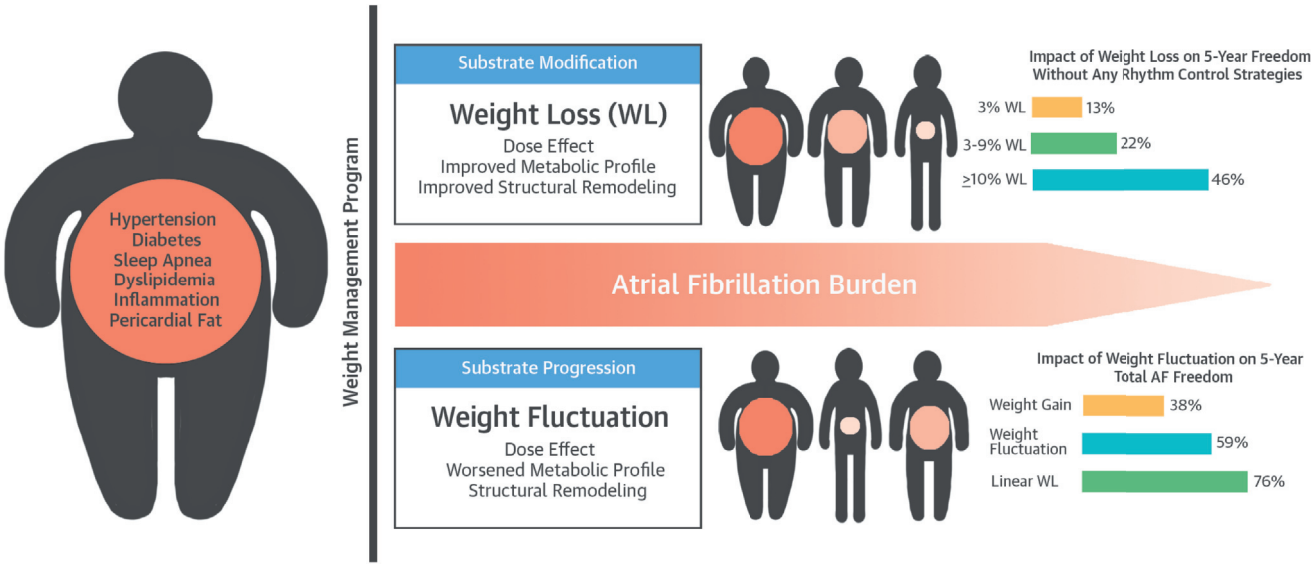
TABLE 3 Weight Fluctuation

	<2% WF Group (N = 54)			2%-5% WF Group (N = 68)			> 5%WF Group (N = 57)			
	Baseline	Follow-Up‡	p Value*	Baseline	Follow-Up‡	p Value*	Baseline	Follow-Up‡	p Value*	p Value†
BMI, kg/m^2	32.6 ± 4.7	29.2 ± 4.8	<0.001	33.3 ± 3.9	30.9 ± 4.5	<0.001	32.3 ± 4.0	31.8 ± 4.8	0.10	<0.001
Mean SBP, mm Hg	147 ± 21	130 ± 14	<0.001	146 ± 17	132 ± 13	<0.001	146 ± 16	140 ± 14	0.01	0.002
DM with HbA_{1c} ≥7	16 (29)	4 (7)	–	18 (26)	9 (13)	–	14 (25)	6 (11)	–	0.056
Medication use										
Anti-HTN	1.0 ± 0.8	0.6 ± 0.6	0.04	1.0 ± 0.9	0.6 ± 0.5	0.01	0.9 ± 1.1	0.9 ± 0.7	1.00	0.037
On lipid Rx	27 (50)	19 (35)	–	29 (43)	21 (31)	–	32 (56)	33 (57)	–	0.04
AA	1.0 ± 0.8	0.4 ± 0.6	<0.001	1.2 ± 0.7	0.3 ± 0.5	<0.001	0.9 ± 0.7	0.3 ± 0.5	<0.001	0.21
Serology and lipid profile										
hsCRP, mg/l	3.4 ± 3.5	1.6 ± 2.3	0.001	5.5 ± 11.6	2.8 ± 3.8	0.05	3.3 ± 6.1	4.4 ± 5.7	0.35	0.05
Fasting insulin level, mU/l	17.7 ± 7.7	12.5 ± 9.5	0.08	17.4 ± 5.6	12.5 ± 10.0	0.001	12.3 ± 5.8	14.5 ± 8.9	0.23	0.01
LDL level, mg/dl	108 ± 31	89 ± 23	<0.001	116 ± 35	92 ± 27	<0.001	104 ± 35	112 ± 31	0.12	<0.001
HDL level, mg/dl	46 ± 11	54 ± 15	<0.001	46 ± 15	54 ± 15	<0.001	46 ± 11	46 ± 15	0.39	0.01
TG level, mg/dl	133 ± 53	106 ± 44	<0.001	141 ± 53	115 ± 53	0.003	141 ± 80	141 ± 71	0.91	0.02
Total cholesterol, mg/dl	185 ± 35	162 ± 31	<0.001	189 ± 35	162 ± 31	<0.001	178 ± 46	174 ± 35	0.21	0.02
Echocardiogram										
Indexed LA volume, ml/m^2	37.4 ± 4.9	32.2 ± 7.2	<0.001	38.4 ± 4.3	33.8 ± 8.0	<0.001	39.2 ± 4.2	39.8 ± 6.5	0.55	<0.001
IV septum, mm	12.0 ± 2.0	11.1 ± 1.2	<0.001	11.5 ± 2.0	11.0 ± 2.0	0.01	11.4 ± 2.0	11.2 ± 2.0	0.59	0.04
LVEDD, cm	4.9 ± 0.6	4.7 ± 0.7	0.05	4.9 ± 0.5	4.7 ± 0.7	0.05	5.0 ± 0.6	5.0 ± 0.6	0.71	0.13
Lateral E/E' ratio	11.9 ± 3.5	9.4 ± 3.8	<0.001	12.5 ± 4.0	10.4 ± 4.8	0.01	12.1 ± 3.9	12.7 ± 5.2	0.42	0.005

Values are mean ± SD or n (%). Impact of weight fluctuation on cardiac risk factors and cardiac structure from baseline to follow-up. *p Value refers to within group difference (baseline to follow-up). †p Value refers to between group differences over time (group-time interaction). ‡Median follow-up: 48.4 ± 18.2 months for group 1, 46.0 ± 16.7 months for group 2, and 48.3 ± 18.4 months for group 3.

WF = weight fluctuation; other abbreviations as in Tables 1 and 2.

CENTRAL ILLUSTRATION **Weight Management and Atrial Fibrillation**



Pathak, R.K. et al. J Am Coll Cardiol. 2015; 65(20):2159–69.

(Left) Obesity is associated with a variety of associated comorbidities. These are all associated with progression of the atrial substrate and the development of atrial fibrillation (AF). **(Top)** A dedicated weight management program with weight loss (WL) is associated with reverse remodeling of the atrial substrate and a dose-dependent reduction in the AF burden, which is sustained in the long term. **(Bottom)** The consequence of weight fluctuation, which somewhat curtails the beneficial effects of WL.

Obesity is associated with structural and electrical remodeling of the atria that forms the substrate in the development and progression of AF (19,20). Weight loss results in reversal of atrial dilation and left ventricular hypertrophy, as well as a marked reduction of AF symptoms and arrhythmia burden (14). However, controversies exist regarding the long-term sustainability of weight loss (21). In the present study, progressive and linear weight loss of ≥10% was associated with marked improvement in long-term freedom from AF. Previously symptomatic AF patients (45.5%) no longer required antiarrhythmic medications or ablation. In this study, 66% of the patients who lost ≥10% weight maintained the weight loss at long-term follow-up. Notably, participation in a dedicated weight management clinic was associated with higher weight loss maintenance. These results highlight the central role of a dedicated weight management clinic in treating overweight and obese patients with AF.

Our data provided a unique opportunity to ascertain the effect of weight fluctuation during the weight loss process. Our results revealed that >5% weight fluctuation lessened the benefit conferred by weight loss. This effect of weight fluctuation on AF recurrence risk remained significant despite adjusting for baseline weight, and was in accord with previous studies that showed that weight fluctuation was associated with an increased risk of hypertension and diabetes, as well as an increase in other cardiometabolic traits (22–25). Weight fluctuation occurred significantly less often in patients who regularly attended the dedicated weight management clinic. Patient engagement and collaborative involvement improved treatment plan adherence and persistence, and might be “the forgotten piece” in the compliance puzzle.

It is probable that multiple mechanisms contributed to the impact of weight loss on reduction of AF burden. Obesity clusters with other cardiovascular risk factors, including impaired glucose tolerance, dyslipidemia, hypertension, and sleep apnea (26,27), which are all associated with an increased AF risk in the general population (12,13,28). Intentional weight loss in obese patients systematically reduces these allied risk factors (29–33). In this study, we observed the beneficial effects of weight loss on BP, diabetic control, the lipid profile, and inflammation, all of

which might have contributed to reduction of the AF burden. Our previous work demonstrated that short-term weight loss and other risk factor management resulted in a reduction of the AF burden (14,15). The present study demonstrated that these beneficial effects on AF burden persisted during long-term follow up, were dose-dependent, but were also partially offset in the face of significant weight fluctuation.

STUDY LIMITATIONS. This study has the potential for bias inherent to observational studies. However, measurement bias was reduced through standardized processes in our clinic, and the evaluation by operators was blinded to the patient's weight management regimen. AF burden assessment using 7-day Holter monitoring might miss some AF episodes. However, this was utilized for AF freedom assessment in both the groups and was a limitation for all groups. Ascertainment bias was reduced through the routine collection of outcome data. Importantly, the impact of weight fluctuation on AF burden could not be evaluated by a randomized design. Finally, weight loss resulted in improvement in various associated risk factors, such as sleep apnea and BP. This study did not provide insight into the relative contribution of each risk factor.

CONCLUSIONS

Sustained weight loss, particularly with avoidance of weight fluctuation, is associated with a dose-dependent reduction in AF burden and maintenance of sinus rhythm. This occurs in conjunction with favorable changes in the cardiometabolic risk factor profile, inflammatory state, and cardiac remodeling.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Weight loss is associated with a reduction in the burden and symptomatic severity of AF, but weight fluctuations >5% have an adverse effect that is associated with a greater likelihood of recurrent AF.

COMPETENCY IN PATIENT CARE: A physician-led clinic focused on engaging patients in management of excess body weight and related cardiovascular risk factors promotes sustained weight loss, reduces weight fluctuations, and is associated with greater long-term freedom from recurrent AF.

TRANSLATIONAL OUTLOOK: Additional studies are needed to determine whether weight loss programs and/or procedures in susceptible individuals could prevent or delay the onset of AF, ameliorate the associated atrial pathology, and avoid or reduce the need for anticoagulation to prevent stroke.

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KEY WORDS ablation, atrial fibrillation, cardiac risk factors, obesity, outcomes, remodeling

APPENDIX For details on the various protocols used in this study, please see the online version of this article.